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# Risk Management in the United States

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Division of Risk Management,  
Food and Drug Administration

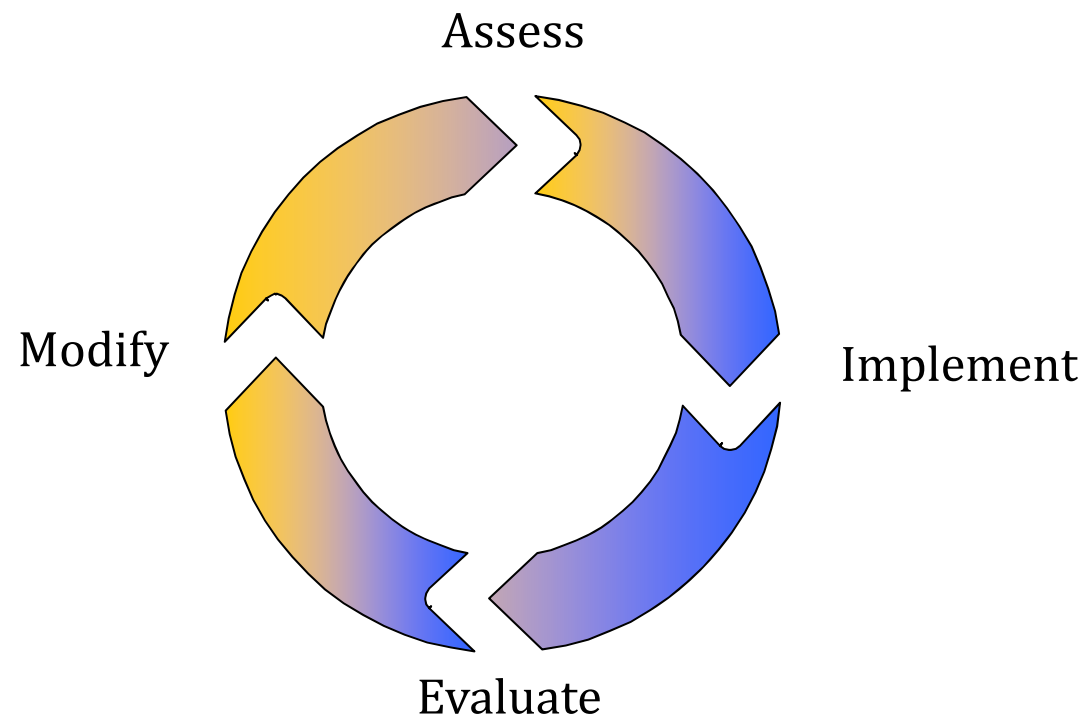
# Objectives

- Be able to:
  - Describe the history of drug Risk Management in the US to date
  - Describe the considerations in determining the need for a REMS
  - Describe the elements of a REMS
  - Describe the assessment requirements of REMS
  - Describe the elements of specific REMS that mitigate the potential for medication errors

# What is Risk Management?

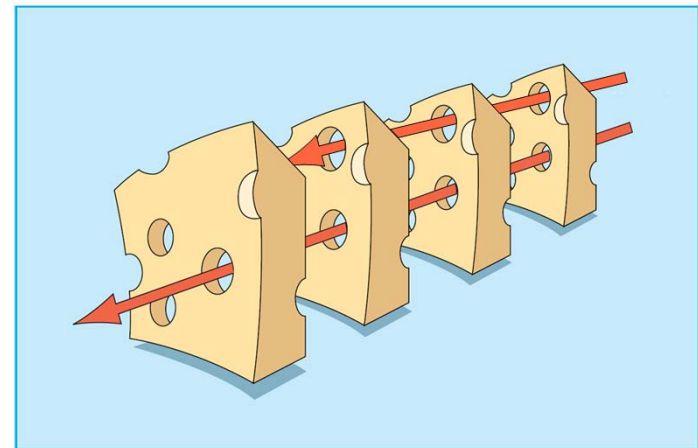
## Risk Management Concept

**Risk assessment + Risk minimization = Risk management**



# Risk mitigation

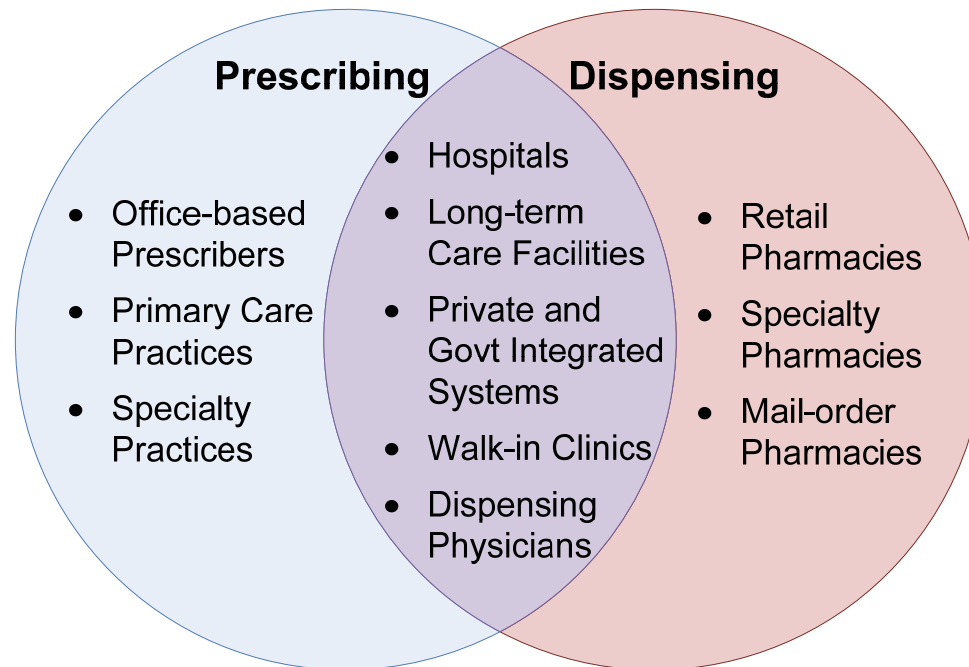
- Risk mitigation is often accomplished by introduction of a series of steps or processes that lower likelihood of unsafe use
  - May reinforce good clinical practices
  - May introduce new risk mitigation measures
  - May include administrative checks to support risk mitigation efforts
- Each intervention that is part of risk mitigation may introduce some level of burden



Adapted from: Reason J. Human Error: Models and Management. *British Medical Journal* 2000

# Recognize diversity in the healthcare system

- Healthcare system is diverse and processes differ across settings



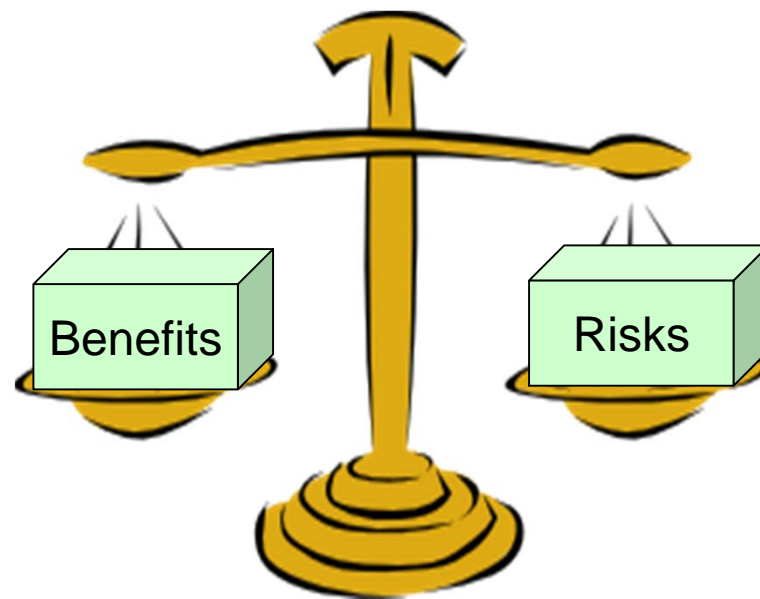
# The foundation of risk management for drugs and therapeutic biologics

- Product safety issues are typically managed through:
  - Labeling is the cornerstone of risk management and the foundation for the risk management of products
  - Routine reporting requirements allows us to continually assess the benefit risk profile of the product



## Why do we need additional risk management tools?

- In a small number of drugs/biologics, additional measures are necessary to mitigate risks and preserve benefits.





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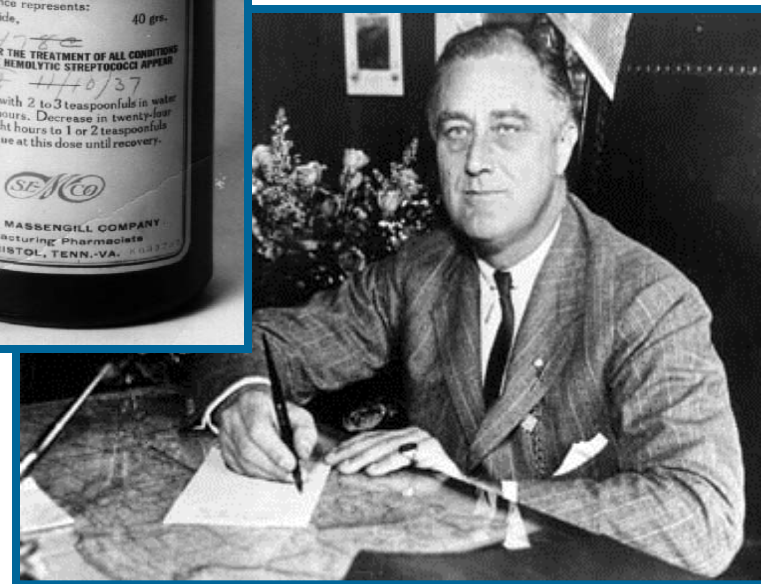
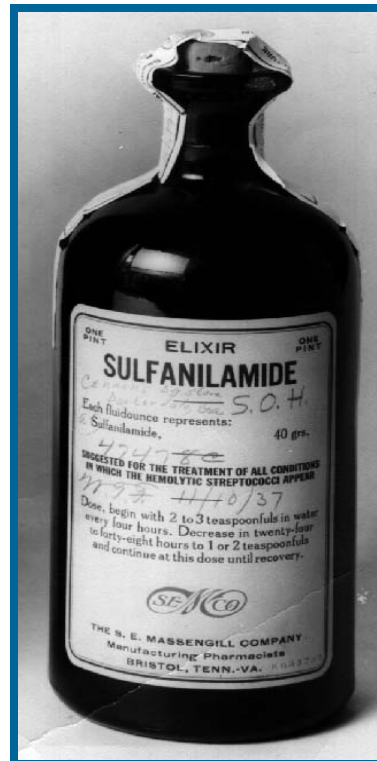
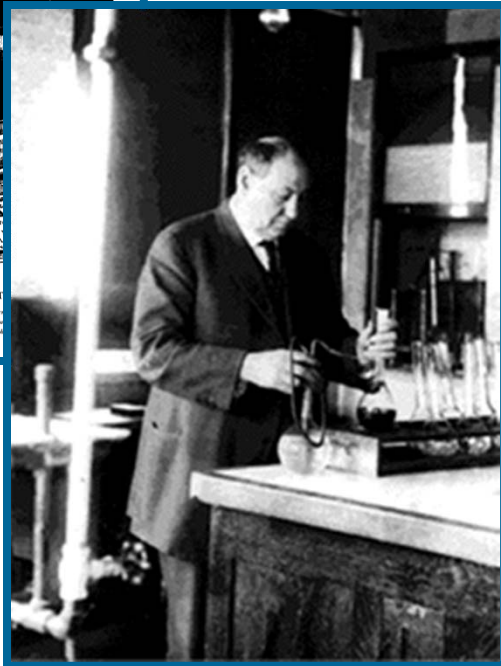
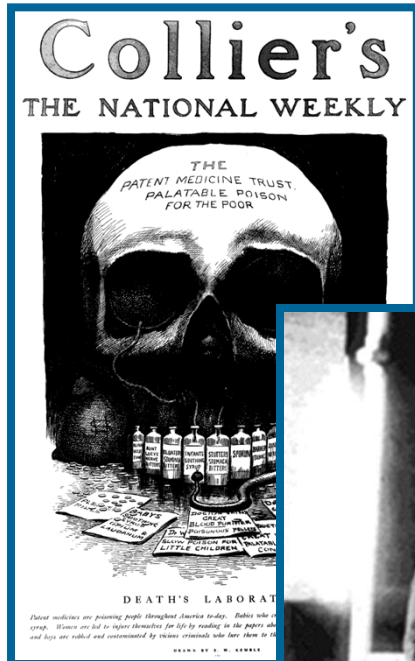
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# Risk Management for Drugs in the U.S.





# The Past...

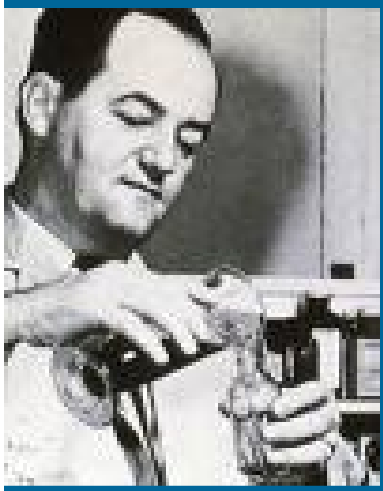


# The Past...



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1906: Pure Food and Drug Act

1938:

Food, Drug, and Cosmetic Act

1951:

1962:

1970:

Prohibited interstate commerce of adulterated or misbranded drugs (identified the US Pharmacopeia and the National Formulary as the official standards for Drugs)

- Required the presence and amount of selected dangerous or addicting substance be labeled
- Enabled the government to take action against illegal products

1970s:

1980-1990s

1998:

1998:

1999:

## Limitations

- Failed to regulate medical devices and cosmetics and did not provide authority to conduct factory inspections
- No ability to control what drugs could be marketed

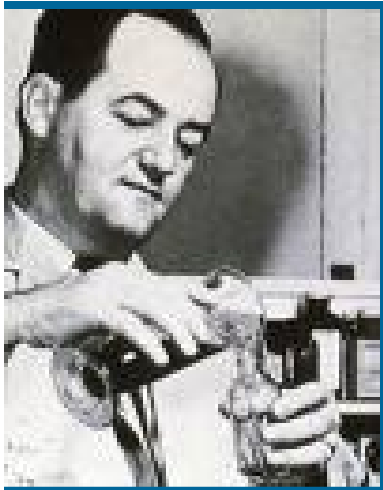


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1906: Pure Food and Drug Act

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1951: Durham-Humphrey Amendment

1962:

1970:

Firms had to **PROVE** to FDA that any new drug was **SAFE** before it could be marketed – the birth of the “new drug application”



1970s:

1980-1990s:

1998:

1998:

1999:

Invigorated by the 107 deaths caused by the elixir sulfanilamide (containing diethylene glycol (antifreeze)).

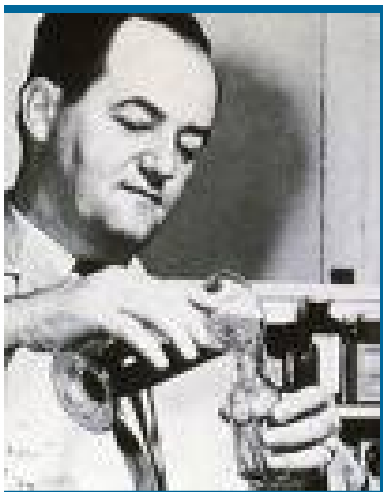
Included regulation of cosmetics and devices, authorized factory inspections, and outlawed bogus therapeutic claims

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1938: Food, Drug and Cosmetic Act

1951: Durham-Humphrey Amendment

1962: Kefauver-Harris Amendment

1970: Defines the kinds of drugs that cannot be used safely without medical supervision and restricts their sale to prescription by a licensed practitioner

1970s: Methadone distribution restricted to patients treated for opioid addiction

1980-1990s: FDA develops first risk management programs

1998: Adverse Event Reporting System (AERS)

1998: Medication Guide regulation (21 CFR 208)

1999: FDA publishes *Managing the Risks from Medical Product Use*

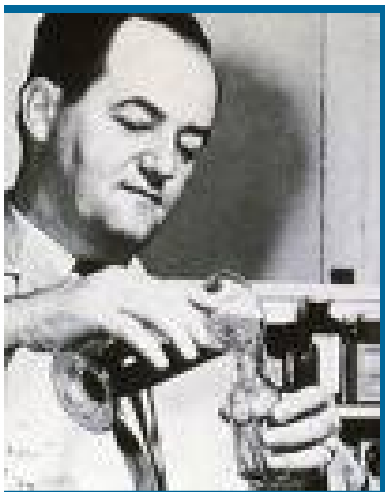


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1970: FDA requires the first patient package insert

Dr. Frances Kelsey - FDA medical officer in charge of thalidomide review and believe the data were incomplete to support the safety of the drug

1970s:

1980-1990s: F Manufacturers had to **PROVE** to FDA that their drugs were **EFFECTIVE AND SAFE** before they could go to market

1998:

1998: Medication Guide regulation (21 CFR 208)

1999: FDA publishes *Managing the Risks from Medical Product Use*



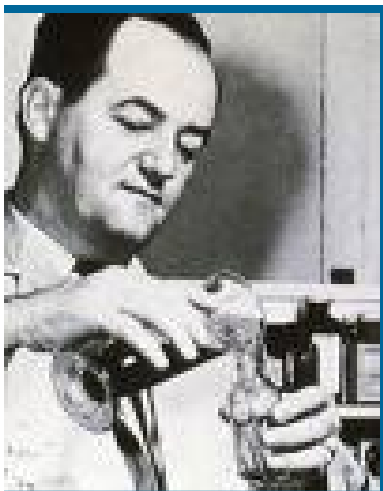


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1970: FDA requires the first patient package insert  
The Comprehensive Drug Abuse Prevention and Control Act



1970s: Methadone distribution restricted to patients treated for

1980-1990s: First patient package insert is required for Oral contraceptives, which must contain information for the patient about specific risks and benefits

1998: A

1998: M Categorizes drugs based on abuse and addiction potential and medical value

1999: F

Use

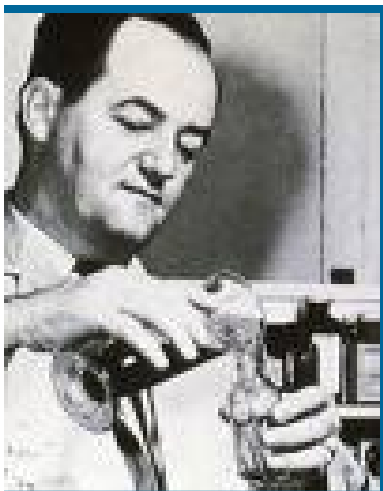
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1998:

M FDA develops restricted distribution programs

1999: FDA publishes *Managing the Risks from Medical Product Use*

## Early risk management programs (RMP): Accutane® (isotretinoin) Pregnancy Prevention Program

- Approved indication (US): severe recalcitrant nodular acne (1982)
  - Pregnancy Category X
- 1988 Dermatologic Advisory Committee meeting
- Pregnancy Prevention Program elements included:
  - Boxed warning
  - Informed Consent for female patients
  - Pregnancy Prevention Program Kit for prescribers
  - Accutane Survey and Prescriber Tracking Survey
  - Educational efforts
  - REMS Approved 10/2010





# Clozaril® (clozapine): No Blood, No Drug

- 1st in class atypical antipsychotic
- Approved indications (US)
  - Treatment resistant schizophrenia (1989)
  - Reducing the risk of recurrent suicidal behavior in schizophrenia or schizoaffective disorders (2002)
- Boxed warning: Agranulocytosis
- Restricted distribution
  - Enrollment of prescribers and pharmacies
  - Mandatory weekly WBC monitoring
  - Patient registration in Clozaril National Registry (CNR)
  - REMS Approved 9/2015

# Thalomid® (thalidomide): S.T.E.P.S. Program

- Approved indications (US)
  - Erythema nodosum leprosum (1998)
  - Multiple myeloma (2006)
- System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.)
- Restricted distribution requirements:
  - Enrollment of prescriber, pharmacy, and all patients
  - Pregnancy testing + use of reliable contraception
  - Telephone survey by prescribers and patients
  - Voluntary survey of subset of FCBP
  - REMS Approved 8/2010

CAUSES BIRTH DEFECTS

DO NOT  
GET PREGNANT

# The Past...

June 2002: Prescription Drug User Fee Act (PDUFA) III

Feb 2005: Drug Safety Oversight Board

Mar 2005: FD

Sept 2006: IOI

an

Mar 2007: FD

Co

June 2007: Pu

Sept 2007: PD

## PDUFA III: 2002-2007

User fees for drug safety and risk management activities. These activities include:

- Review of pre-NDA/BLA meeting packages and meeting with industry
- Review of proposed risk management plans and protocols for observational studies submitted with NDA/BLA
- Development of guidances that address good risk assessment, risk management, and pharmacovigilance





# The Past...

June 2002: Prescription Drug User Fee Act (PDUFA) III

Feb 2005: Drug Safety Oversight Board

Mar 2005: FDA finalizes 3 risk management guidances

Sept 2006: IOI  
an  
Consists of FDA staff and representatives from Federal partners (e.g., Department of Defense, Veterans Administration, etc)

Mar 2007: FD  
Co  
Board advises the FDA CDER Director on drug safety issues and work with the agency in communicating safety information to health professionals and patients

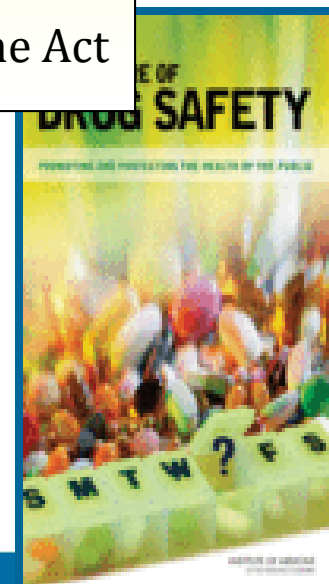
June 2007: Pu

Sept 2007: PDUFA (IV) / PDUFA



# The Past...

June 2002:	Prescription Drug User Fee Act (PDUFA) III	Amended Federal Food, Drug, and Cosmetic Act (FDCA)
Feb 2005:	Drug	
Mar 2005:	FDA	Provided FDA the <u>legal authority</u> to require <b>risk evaluation and mitigation strategies (REMS)</b> for applicable drugs
Sept 2006:	IOM and P	<ul style="list-style-type: none"> <li>• May not introduce drug into interstate commerce if in violation of provisions</li> <li>• Drug may be found to be misbranded</li> <li>• FDA can impose civil penalties for violations of the Act</li> </ul>
Mar 2007:	FDA Com	
June 2007:	Public RISKMAP workshop	
Sept 2007:	PDUFA (IV) / FDAAA	



# Restricted Distribution Programs Prior to FDAAA

- |         |                                 |         |  |
|---------|---------------------------------|---------|--|
| • 1988: | Isotretinoin*                   | • 2002: | Alosetron  |
| • 1989: | Clozapine                       | • 2002: | Sodium oxybate                                     |
| • 1998: | Thalidomide<br>Fentanyl citrate | • 2003: | Abarelix   |
|         |                                 | • 2005: | Lenalidomide                                       |
| • 1999: | Dofetilide                      | • 2006: | Natalizumab<br>Fentanyl PCA                        |
| • 2000: | Mifepristone                    |         |  |
| • 2001: | Bosentan                        | • 2007: | Ambrisentan<br><br>Small pox (Vaccinia)<br>Vaccine |

\* *RiskMAP for isotretinoin was approved in 1988 and revised in 2002 & 2005.*

# Knowledge Check

- REMS Came into existence via the following legislation:
  - A. FDA Amendments Act of 2007
  - B. Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012
  - C. FDA Compliance Regulation of 1997
  - D. Omnibus Budget Reconciliation Act of 1990

# Knowledge Check

- REMS Came into existence via the following legislation:
  - **A. FDA Amendments Act of 2007**
  - B. Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012
  - C. FDA Compliance Regulation of 1997
  - D. Omnibus Budget Reconciliation Act of 1990



# Risk Evaluation and Mitigation Strategy (REMS)

- A required risk management plan that uses risk mitigation strategies beyond FDA-approved FDA professional labeling.
- FDA Amendments Act of 2007 authorized FDA to require sponsors to develop and comply with REMS programs if determined necessary to ensure the benefits outweigh the risks.
  - *FDA does not directly regulate healthcare professionals or patients who may be impacted by a REMS.*
- Applies to NDAs, BLAs, and ANDAs.
- REMS can be required pre- or post-approval.

# Risk Evaluation and Mitigation Strategy (REMS) - continued

- Designed to achieve specific goals to mitigate risks associated with use of a drug.
- FDA specifies the required elements of a REMS.
- Drug sponsors develop the REMS program based on required elements. FDA reviews and approves the REMS.
- Each REMS has specific safety measures that are targeted to the serious risk(s) associated with the drug or class of drugs.
- All REMS include elements, communication, and/or educational materials to communicate risk information to various stakeholders.

# Considerations in determining the need for a REMS

- Estimated size of the population likely to use the drug
- Seriousness of the disease or condition being treated
- Expected benefit of the drug
- Duration of treatment
- Seriousness of any known or potential adverse effects
- Drug is a new molecular entity



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# Components of a REMS

# Content of a REMS

- Goal(s) of a REMS
  - All REMS should include a statement of one or more goals
  - If element(s) to assure safe use (ETASU), must include one or more goals to mitigate a serious risk listed in the labeling
  - Assessments of approved REMS should measure whether the goals are being met

# Possible Components of a REMS

- A REMS can include
  - Medication Guide or Patient Package Insert
  - Communication Plan for Healthcare Providers (HCPs)\*
  - Elements to Assure Safe Use (ETASU)
  - Implementation System
- Must include a timetable for submission of assessments of the REMS\*



*\*Note: This requirement applies to NDAs and BLAs only. ANDAs (generics) are not required to include a timetable for submission of assessments for REMS*

# Medication Guides



- Provide FDA approved patient-friendly labeling
- Can be required as part of labeling, if FDA determines one or more:
  - Patient labeling could help prevent serious adverse events
  - The product has serious risks that could affect patient's decision to use or continue to use
  - Patient adherence to directions is crucial to product effectiveness
- To be included in the REMS, it must be determined that the MG is necessary to ensure the benefits outweigh the risks- it can be a REMS element or a tool under another element of the REMS\*

\* February 2011 Guidance available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM244570.pdf>

# Communication Plan

- FDA approved materials used to aid sponsor's implementation of REMS and/or inform healthcare providers about serious risk(s)
- Communication plans may include:
  - “Dear Healthcare Professional” letters
  - Informational brochures, Slide deck
  - Information pieces placed in professional journals or made available at scientific meetings
  - Training materials, videos
  - Dissemination of information to HCPs through professional societies
  - Information about the REMS to encourage implementation



IMPORTANT  
DRUG  
WARNING



# Elements to Assure Safe Use (ETASU)

- Requirements and other actions that healthcare providers, patients, or other stakeholders need to execute prior to prescribing or dispensing the drug to the patient. Some actions may also be required in order for the patient to continue on treatment.

## Purpose of REMS with ETASU

### FDAAA Title IX Section 901 505-1 f(1)(A)

- **(f) Providing Safe Access For Patients To Drugs With Known Serious Risks That Would Otherwise Be Unavailable**
- (1)(A) the drug, which has been shown to be effective, but is associated with a serious adverse drug experience, can be approved only if, or would be withdrawn unless, such elements are required as part of such a strategy to mitigate a specific serious risk listed in the labeling of the drug.

# Elements to Assure Safe Use (ETASU)

- Specific elements:
  - A. Certification and specialized training of HCPs who prescribe the drugs
  - B. Certification of pharmacies or other dispensers of the drug
  - C. Dispensing/administration of drug in limited settings e.g., hospitals
  - D. Drug is dispensed/administered only with evidence of safe-use conditions
  - E. Each patient using the drug is subject to certain monitoring
  - F. Enrollment of treated patients in registries
- Are not mutually exclusive

# Implementation Systems

- REMS may include an implementation system related to these ETASUs:
  - Certification of pharmacies and hospitals
  - Restricted use to certain healthcare settings
  - Documentation of safe use conditions
- May require applicant to take reasonable steps to
  - Monitor and evaluate implementation of such elements by health care providers, pharmacists, and other parties in the health care system who are responsible for implementing such elements; and
  - Work to improve implementation of such elements by such persons

## Timetable for Submission of Assessments

- REMS for an NDA or BLA product must have a timetable for submission of assessments of the REMS
- The timetable for submission of assessments must include an assessment
  - by 18 months,
  - by 3 years, and
  - in the 7th year after the REMS is initially approved
- Can be eliminated after 3 years

# REMS Assessment Plan

- Objective: to gather sufficient information to determine whether the REMS is meeting its goals
- Sponsor's plan to assess the REMS may include:
  - Proposed evaluation methods and the rationales for the chosen measures
  - Targeted values for each measure and the timeframe for achieving them
  - Type of data that will be collected
  - Plans to assess unintended and/or unfavorable consequences of the REMS following implementation

# Information that might be used to assess REMS

- A survey to evaluate patients' or HCPs' knowledge of the serious risks or measures that need to be taken to mitigate risk
- Enrollment/certification statistics kept by company
- Information about use patterns of the drug including:
  - Use by prescriber specialty
  - Patient-level data (age, gender, race)
  - Length of therapy
  - Indication
  - Concomitant drug therapy

# Information that might be used to assess REMS (continued)

- Population-based administrative or claims-based data to measure rates of specified serious adverse events
- Active surveillance using sentinel reporting sites to determine rates of specified serious adverse events
- Summaries of specific adverse events collected spontaneously



# Knowledge Check

- Considerations in determining the need for a REMS include the following:
  - A. Duration of treatment
  - B. Estimated Size of the Population expected to use the drug
  - C. Patent status of the molecule
  - D. A & B

# Knowledge Check

- Considerations in determining the need for a REMS include the following:
  - A. Duration of treatment
  - B. Estimated Size of the Population expected to use the drug
  - C. Patent status of the molecule
  - **D. A & B**

# Knowledge Check

- Potential Elements of a REMS include:
  - A. Communication Plan
  - B. Medication Guide
  - C. Elements to Assure Safe Use
  - D. A, B, and C

# Knowledge Check

- Potential Elements of a REMS include:
  - A. Communication Plan
  - B. Medication Guide
  - C. Elements to Assure Safe Use
  - **D. A, B, and C**

# Knowledge Check

- Assessments of REMS must be completed by:
  - A. 18 months post approval
  - B. 3 years post approval
  - C. 7 years post approval
  - D. A, B and C if the REMS is not released by year 3

# Knowledge Check

- A. 18 months post approval
- B. 3 years post approval
- C. 7 years post approval
- **D. A, B and C if the REMS is not released by year 3**



# Examples of REMS- an in-depth look

# Medication Error

- A medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. – NCCMERP



# Transmucosal Immediate-Release Fentanyl Products (TIRF)

Purpose of REMS:	to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors
Certification process:	Authorized Representative must complete the TIRF REMS Access Education Program, knowledge assessment questions, and sign an enrollment form
Pharmacy requirements:	Verify prescriber is certified Verify patient is not inactivated Dispense with Medication Guide
Dispensing limitations:	Follow state dispensing requirements
Additional comments:	REMS includes Abstral, Actiq, Fentora, Lazanda, Onsolis, Subsys, and applicable generics Dispense authorization can be obtained by using pharmacy management system or by contacting the REMS program

# Transmucosal Immediate-Release Fentanyl Products (TIRF) (Continued)

- TIRF REMS Access Education Program
  - Prescribers
  - Pharmacists
- Examples of medication error mitigation:
  - Appropriate Patient Selection and definition of opioid-tolerant
  - Appropriate Conversion
  - Patient Counseling Information
    - Emphasizes concepts that were historically not well-understood by patients



# Examples of REMS that mitigate other risks....

# Blincyto (blinatumomab)

<b>Purpose of REMS:</b>	<p>mitigate the risk of cytokine release syndrome which may be life threatening or fatal;  the risk of neurological toxicities which may be severe, life-threatening, or fatal;  and the risk of preparation and administration Errors <u>by informing</u></p>
<b>Communication Plan:</b>	<p>REMS Letter for Healthcare Providers  REMS Letters for:  - Hospital and Home Healthcare Pharmacists  - Professional Societies  REMS Fact Sheet  Dissemination of Info at Scientific Meetings</p>

## Blinicyto (continued)

- Letters contain the following information to direct the healthcare community to the Package Insert Labeling:
  - *It is very important that the instructions for preparation (including admixing) and administration are strictly followed to minimize medication errors (including underdose and overdose).*



## iPledge:

<b>Purpose of REMS:</b>	<b>To mitigate the risk of teratogenicity</b>
<b>Certification process:</b>	Responsible site pharmacist completes the Pharmacy Enrollment Form
<b>Pharmacy requirements:</b>	Review Pharmacist Guide for the iPledge Program Verify prescriber is certified Verify patient is enrolled Obtain an Risk Management Authorization (RMA) Dispense with Medication Guide
<b>Dispensing limitations:</b>	30-day supply; no refills allowed
<b>Additional comments:</b>	RMA can be obtained using a voice-based system or web-based system Document the RMA on each prescription REMS covers all FDA approved products that include isotretinoin

# iPledge

- Prescriber Training Brochure
- Pharmacy Training
- Patient Enrollment
- Patient Counseling tools and guides (Safe Use Condition)
- Medication Guide

**Tools are designed to mitigate the risk of fetal exposure to isotretinoin**

## Knowledge Check

- Components of a REMS which may mitigate medication errors include
  - A. Prescriber training slide decks
  - B. Medication Guides
  - C. Factsheets
  - D. Safe Use Condition Patient Counseling
  - E. A, B, C, and D



# Knowledge Check

- Components of a REMS which may mitigate medication errors include
  - A. Prescriber training slide decks
  - B. Medication Guides
  - C. Factsheets
  - D. Safe Use Condition Patient Counseling
  - **E. A, B, C, and D**

# Summary

- Risk management continues throughout the lifecycle of a product
- For the majority of approved products, labeling and routine reporting requirements are sufficient to mitigate risks and preserve benefits
- Tools selected for a risk management program are product specific
- REMS contain elements and appended materials to mitigate specific risks associated with a drug, and the TIRF REMS attempts to mitigate medication errors associated with transmucosal immediate-release fentanyl products



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# The End